Heart failure with preserved ejection fraction: everything the clinician needs to know

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Heart failure with preserved ejection fraction (HFpEF) is increasingly recognised and diagnosed in clinical practice, a trend driven by an ageing population and a rise in contributing comorbidities, such as obesity and diabetes. Representing at least half of all heart failure cases, HFpEF is recognised as a complex clinical syndrome. Its diagnosis and management are challenging due to its diverse pathophysiology, varied epidemiological patterns, and evolving diagnostic and treatment approaches. This Seminar synthesises the latest insights on HFpEF, integrating findings from recent clinical trials, epidemiological research, and the latest guideline recommendations. We delve into the definition, pathogenesis, epidemiology, diagnostic criteria, and management strategies (non-pharmacological and pharmacological) for HFpEF. We highlight ongoing clinical trials and future developments in the field. Specifically, this Seminar offers practical guidance tailored for primary care practitioners, generalists, and cardiologists who do not specialise in heart failure, simplifying the complexities in the diagnosis and management of HFpEF. We provide practical, evidence-based recommendations, emphasising the importance of addressing comorbidities and integrating the latest pharmacological treatments, such as SGLT2 inhibitors.

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Introduction

Heart failure with preserved ejection fraction (HFpEF), simply put, is when a person has a diagnosis of heart failure and their left ventricular ejection fraction (LVEF) is 50% or higher. The definition of HFpEF offered by the European Society of Cardiology (ESC) is more complex: "Those with symptoms and signs of HF [heart failure], with evidence of structural and/or functional cardiac abnormalities and/or raised natriuretic peptides (NPs), and with an LVEF ≥50%, have HFpEF".[1] This nuanced and lengthy definition makes it more difficult to diagnose HFpEF than heart failure with reduced ejection fraction (≤40%) or mildly reduced ejection fraction (41–49%). One example of the challenge of diagnosing HFpEF is that approximately 20% of patients with HFpEF (mostly those living with obesity) have normal natriuretic peptide levels.[2] Therefore, there is no one simple definition that specifies a combination of imaging or natriuretic peptides that gives a binary rule-in or rule-out assessment of whether a person has HFpEF.

Clinical trials of HFpEF have adopted a simple definition of HFpEF (table). Typically, this definition includes a combination of LVEF more than 40% (although HFpEF is technically defined as ≥50%) and elevated N-terminal pro-B type natriuretic peptide (NT-proBNP) levels (usually above 300 pg/mL in sinus rhythm and 600 pg/mL in atrial fibrillation) in combination with a structural abnormality (usually left ventricular hypertrophy or an enlarged left atrium) on echocardiography. Many clinicians use this combination to diagnose HFpEF in clinical practice; however, guidelines use LVEF greater than 50% as the cut-point and also recommend functional abnormality assessment with tissue Doppler imaging to define increased left ventricular stiffness with impaired relaxation, and increased left ventricular filling pressures.[1]

Epidemiology

Because of a growing and ageing population and increasing prevalence of conditions that contribute to the pathophysiology of HFpEF, such as obesity, hypertension, and diabetes, the total number of patients living with HFpEF continues to rise.[5] In high-income countries, the prevalence of known heart failure is generally estimated at 1–2% of the general adult population, with an estimated 50% of those having HFpEF. However, these estimates are largely based on administrative claims data or electronic health records. There are no modern prospective, population-based studies using natriuretic peptides and detailed echocardiography to assess the true prevalence of HFpEF. If such a study were to be conducted, especially with a liberal interpretation of the ESC's definition of HFpEF, it is possible that the prevalence of HFpEF would be much higher than currently cited. A meta-analysis of echocardiographic screening studies in the general population reported a prevalence of all-type heart failure in people aged 65 years

Search strategy and selection criteria

Searches for heart failure with preserved ejection fraction were for material up to Sept 28, 2023 and were restricted to material published in English. Searches were run in PubMed, ClinicalTrials.gov, and the Cochrane Library (Wiley). Search terms included: "randomized controlled trial", "meta-analysis", "systematic reviews", "epidemiological studies", "population studies", "review article", and "editorial". Specific search terms included: "heart failure preserved ejection fraction", "epidemiology", "prognosis", "pathogenesis", "inflammation", "phenotypes", "contributing co-morbidities", "diagnosis", "HFpEF mimics", "congestion management", "SGLT2i", "GLP-1 receptor agonist", "sacubitril/valsartan", "mineralocorticoid receptor agonists", "tirzepatide", "ziltivekimab", "self-care", and "rehabilitation".

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	Left ventricular ejection fraction	Left ventricular hypertrophy	Left atrium enlargement	Elevated filling pressures	Natriuretic peptide level (pg/mL)
EMPEROR-Preserved (2021)[3]	>40%	Septal or posterior wall thickness ≥1·1 cm; left ventricular mass index ≥95 g/m² (women) and ≥115 g/m² (men)	Width ≥4·0 cm; length ≥5·0 cm; area ≥20·0 cm²; volume ≥55 mL or volume index ≥34 mL/m²	E:e' (mean septal and lateral) ≥13; e' (mean septal and lateral) <9 cm/s	NT-proBNP >300 (no atrial fibrillation) or >900 (with atrial fibrillation)
DELIVER (2022)[4]	>40%	Septal or posterior wall thickness ≥1·1 cm	Width (diameter) ≥3·8 cm, length ≥5·0 m; area ≥20 cm²; volume ≥55 mL or volume index ≥29 mL/m²	NA	NT-proBNP ≥300 (no atrial fibrillation or flutter) or ≥600 (with atrial fibrillation or flutter)

e'=early diastolic mitral annulus velocity. E:e'=early diastolic mitral inflow velocity to early diastolic mitral annulus velocity. HFpEF=heart failure with preserved ejection fraction. NA=not applicable. NT-proBNP=N-terminal pro-B type natriuretic peptide. SGLT2i=SGLT2 inhibitor.

Table: **HFpEF definitions in recent clinical trials of SGLT2 inhibitors**

and over in high-income countries of 11·8%, with more than three quarters of these cases being HFpEF. This meta-analysis gives a calculated prevalence of all-type heart failure in the general population of 4·2% (around 3% for HFpEF); twice as high as the typical reported prevalence.[6] Epidemiological data indicate that the prevalence of HFpEF relative to heart failure with reduced ejection fraction (HFrEF) is increasing at a rate of 1% per year, indicating that HFpEF is becoming the most common type of heart failure.[7]

The three signatory epidemiological features of HFpEF are increasing prevalence with advancing age, female sex, and comorbidities that either contribute to the myocardial stiffness (eg, metabolic and inflammatory) or exacerbate the functional abnormality (eg, atrial fibrillation and valve disease). These three factors interact, as women have greater life expectancy, and advancing age accrues comorbidities.

There is considerable international variation in the prevalence of HFpEF and its contributing factors. For example, compared with high-income countries, low-income countries have a higher prevalence of hypertension, which contributes to HFpEF populations being younger.[8]

Sex and socioeconomic status

HFpEF is more common in women, with one study showing women with heart failure had HFpEF in 67% of cases, compared with 42% of men with heart failure having HFpEF.[9] These data support the notion that sex might play a pathophysiological role in this condition.[5] This higher prevalence of HFpEF in women than men might be partly related to obesity and diabetes. Women have obesity more often than men, and the relationship between obesity and incident HFpEF seems stronger in women.[6] Diabetes confers a higher risk for heart failure, mainly driven by HFpEF, in women (relative risk 1·95, 95% CI 1·70–2·22) compared with men (1·74, 95% CI 1·55–1·95).[10]

Low socioeconomic status assessed by all common measures (education, income, occupation, and region) is independently associated with greater risk of incident heart failure, including HFpEF by 62%,[11] possibly related to a higher prevalence of unfavourable behavioural risk factors, including physical inactivity, poor diet, smoking, and medication non-adherence.[12]

Prognosis

Although HFpEF is thought to be associated with better survival than HFrEF based on findings from clinical trial data,[13] most observational studies show that this difference is negligible.[1] Data from the Karolinska–Rennes (KaRen) study of patients with HFpEF revealed mortality rates at 1 (15%), 3 (31%), 5 (47%), and 10 (74%) years.[14] Although the dominant cause of death is cardiovascular in both HFrEF and HFpEF, non-cardiovascular death does assume a greater proportion of deaths in HFpEF.[15]

Previous studies have noted no difference between HFpEF and HFrEF in terms of hospitalisation rate, hospitalisation duration, and the effect on quality of life (QoL).[12] However, more recent data from the ESC Heart Failure Long-Term Registry shows percentages of patients hospitalised for heart failure and all-cause admission in the HFrEF (14·6% and 31·9%), heart failure midrange ejection fraction (8·7% and 22·0%), and HFpEF (9·7% and 23·5%) groups.[16] Atherosclerosis Risk In Communities surveillance data indicated an increase in admissions for acute decompensated heart failure, primarily driven by HFpEF.[17]

Pathogenesis

Originally, HFpEF was viewed as a disorder due solely to abnormalities in left ventricular diastolic function. Our understanding has evolved so that HFpEF is now understood as a systemic syndrome, perhaps partly triggered by inflammation and with important contributions from ageing, lifestyle factors, genetic predisposition, and multiple comorbidities (some of which might be disease drivers; figure 1).

Inflammation

The inflammatory state induced by chronic obstructive pulmonary disease, renal impairment, obesity, diabetes,

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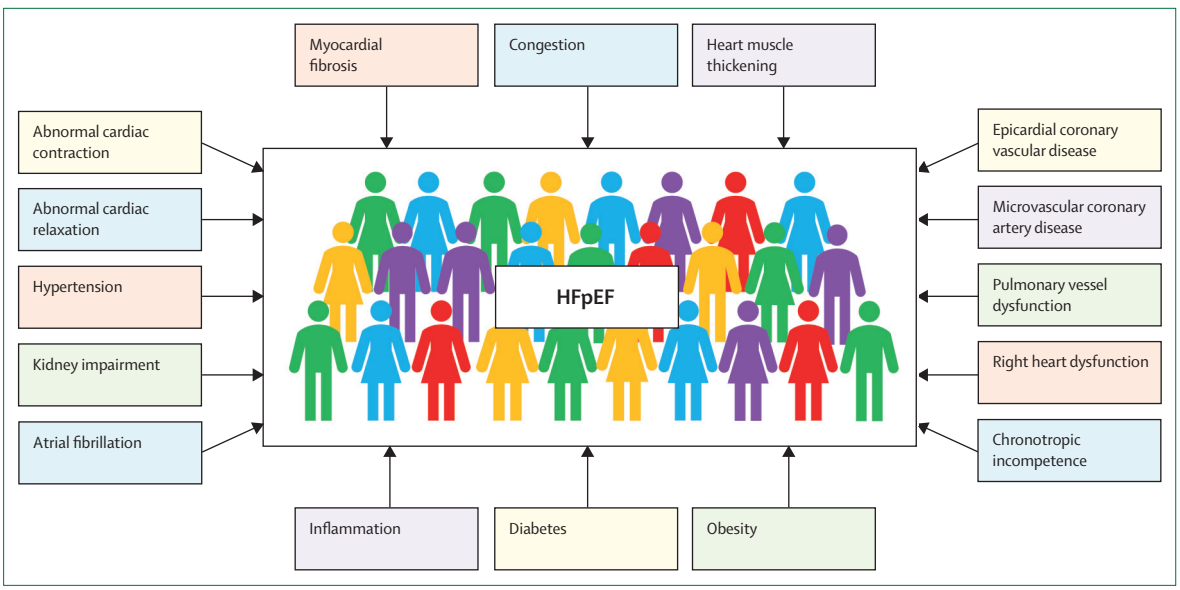

Figure 1: **Interacting causes, contributors, or drivers of HFpEF reflecting the complex and heterogeneous underlying pathophysiology**
HFpEF=heart failure with preserved ejection fraction.

and other comorbidities is predictive of incident HFpEF, but not of HFrEF.[18,19] Inflammation has been proposed as a central mechanism in the pathogenesis of HFpEF.[20] The Paulus theory states that a chronic proinflammatory state, caused by the plethora of comorbidities, results in coronary endothelial inflammation and cardiac dysfunction. Reduced bioavailability of nitric oxide is linked to myocardial and vascular stiffness via the cyclic guanosine monophosphate (cGMP) pathway. This unifying hypothesis is supported by tissue studies of patients with HFpEF showing reduced levels of cGMP.[21] Metabolic disorders and obesity also promote expansion of the epicardial adipose tissue and secretion of adipocytokines, which causes further inflammation and fibrosis of the myocardium. Based on proteomic analyses, there is a strong relationship between inflammatory biomarkers, HFpEF, and extracellular matrix reorganisation.[22] Inflammation affects not only the left ventricle, but also the left atrium, and atrial fibrillation might often be the first sign of HFpEF, especially in patients with obesity or diabetes.[23]

Structural and functional cardiac phenotypes

Although diastolic dysfunction plays a central role in the development of HFpEF, with the impairment in relaxation causing elevated filling pressures at rest or with exertion,[24] multiple non-diastolic abnormalities contribute to the syndrome. These abnormalities include subtle left ventricular systolic dysfunction, left atrial impairment, relative pericardial restraint, abnormal right ventricular-pulmonary artery coupling, pulmonary vascular disease, systemic vascular stiffening, coronary and peripheral microvascular dysfunction, and chronotropic incompetence.[25]

Pulmonary hypertension is very common in HFpEF, seen in roughly 80% of patients, and mortality is increased in this cohort.[26] Some patients will go on to develop pulmonary vascular disease, manifest by elevation in pulmonary vascular resistance and reduction in pulmonary arterial compliance,[27] resulting in reduced exercise capacity and increased risk of adverse outcomes.[28]

Pulmonary hypertension eventually leads to right ventricular systolic dysfunction, which is common and associated with adverse outcomes in HFpEF.[29] However, right ventricular dysfunction can be noted in patients with near normal pulmonary pressures in the setting of atrial fibrillation or tricuspid regurgitation, and can occur during exercise, even when resting function appears normal.[24]

Left atrial remodelling is common in HFpEF and occurs secondary to increased left ventricular filling pressures. Left atrial dysfunction is associated with worse QoL, more pulmonary vascular disease, greater right ventricular dysfunction, reduced exercise capacity, and an increased risk of adverse outcomes, suggesting that patients with greater atrial myopathy might also constitute a different phenotype within the HFpEF spectrum.[30]

Comorbidities contributing to pathophysiology and inflammation

Comorbidity burden is associated with increased severity of HFpEF symptoms and corresponds to a poorer QoL and a worse prognosis.[31] Hypertension, coronary artery disease, obesity, sleep apnoea, diabetes, chronic kidney disease, and atrial fibrillation are risk factors for HFpEF, which are increasing over time.[10,32] Diabetes is a potent risk factor for HFpEF.[33] Importantly, diabetes and obesity

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affect left ventricle function even in the absence of coronary artery disease and hypertension.[34] The rate of obesity is fast on the rise globally, and excess adipose tissue is associated with an increased risk of HFpEF.[35] In the general population, there is a direct relationship between body mass and the parameters of diastolic dysfunction.[36]

Acute myocardial infarction is a driver for developing HFrEF, but chronic coronary artery disease is more related to HFpEF.[37] Both obstructive epicardial coronary artery disease and coronary microvascular dysfunction are very common in HFpEF and often remain undetected.[22]

Another contributing comorbidity is anaemia with a prevalence in HFpEF varying from 12% to 33%.[33,38] Causes of low haemoglobin in patients with HFpEF include iron deficiency, chronic inflammation, and impaired renal function.[39] In an analysis of the TOPCAT trial, patients with HFpEF and anaemia had a higher mortality risk and increased hospitalisations.[40]

Diagnosis

The diagnosis of HFpEF might be fairly straightforward in patients with overt physical examination signs of congestion on physical examination (eg, pitting leg oedema and pulmonary crackles), elevated natriuretic peptide levels (ESC criteria of NT-proBNP >125 pg/mL sinus rhythm) or atrial fibrillation (>365 pg/mL), brain natriuretic peptide (>35 pg/mL sinus rhythm) or atrial fibrillation (> 105 pg/mL), or radiographic evidence of congestion or echocardiographic evidence of elevated filling pressures. Such cases are typically encountered in emergency care settings. However, it is worth noting that even in these overtly congested patients, natriuretic peptide levels can be normal or lower than expected for the given severity of congestion.[41]

In the community, the diagnosis of HFpEF is much more challenging. Patients are at risk of misdiagnosis or under-diagnosis due to several factors, including (1) under-reporting of symptoms by patients (eg, shortness of breath on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea), (2) non-specific heart failure symptoms (eg, fatigue, reduced exercise tolerance, or ankle swelling), (3) absence of awareness of heart failure as a cause of pulmonary symptoms, (4) the presence of mimicking comorbidities, (5) the absence of ready access of natriuretic peptides or echocardiography, and (6) uncertainty on how to diagnose HFpEF (due to uncertainty of how to interpret natriuretic peptide levels and echocardiographic reports). There is a long-standing perception among many clinicians that HFpEF is a condition that causes acute breathlessness with detectable pulmonary and peripheral oedema. There is less appreciation of heart failure as a chronic condition that presents with exercise-related breathlessness and reduced exercise tolerance in the absence of signs of fluid overload. Fluid overload might be absent, particularly in patients receiving diuretics for hypertension. Confusion caused by common comorbidities associated with HFpEF that have overlapping presentations is a frequent clinical scenario (including chronic obstructive pulmonary disease, obesity, type 2 diabetes, ageing, frailty, or deconditioning).[26,42] Collaboration with heart failure specialists can help generalists learn how to diagnose HFpEF. Further confusion can be caused by interpretation of spirometry. Spirometry might show an obstructive pattern due to pulmonary congestion caused by unrecognised heart failure, which further causes misclassification of HFpEF as chronic obstructive pulmonary disease.[43]

Because both type 2 diabetes and heart failure can result in reduced exercise tolerance, and a sedentary lifestyle can mask HFpEF symptoms, HFpEF can remain unrecognised. In a Dutch study of 581 patients older than 60 years with type 2 diabetes not known to have HFpEF, opportunistic screening revealed new heart failure in 27·7% of the participants, the majority of which (22·9%) was HFpEF.[44]

Approximately 20% of patients with HFpEF have normal natriuretic peptide levels.[2] The reason for this finding might relate to the mechanism of natriuretic peptide release. Natriuretic peptides are released in response to high left ventricular diastolic wall stress. Bearing in mind that left ventricular diastolic wall stress is inversely proportional to wall thickness, in cases with mild left ventricular hypertrophy (common in HFpEF), wall stress might be diminished, and pericardial adipose tissue could prevent cardiac stretch, and natriuretic peptides not released as a result.

Another reason for low natriuretic peptide levels is obesity.[45] Patients with obesity and heart failure have lower natriuretic peptide concentrations due to increased expression of clearance receptors and augmented peptide degradation by the adipose tissue.[46] If there is a suspicion of HFpEF in a patient with obesity and low natriuretic peptide levels, referral to a heart failure specialist for HFpEF diagnosis might be warranted.

Therefore, in patients at risk with emerging symptoms, we propose a simple stepwise algorithm to allow for accurate HFpEF diagnosis (figure 2). This algorithm is based around the ESC Heart Failure Guidelines and published HFpEF risk scores.

Step 1: identify a defining feature of HFpEF

This algorithm (figure 2) allows for a diagnosis of HFpEF in most patients (approximately 80%) at step 1 whereby a patient with symptoms, with or without signs, of heart failure, or with an LVEF of 50% or higher has a defining feature (eg, detectable congestion or elevated natriuretic peptide levels), and meets at least one of the echo-cardiographic criteria. Therefore, the need to proceed to step 2 and 3 is rare. For the generalist, moving to step 2 should prompt a referral onward for expert guidance. Guidelines emphasise that the greater the number of non-invasive indicators of raised left ventricular filling pressures, the greater the likelihood of a diagnosis of HFpEF.[1]

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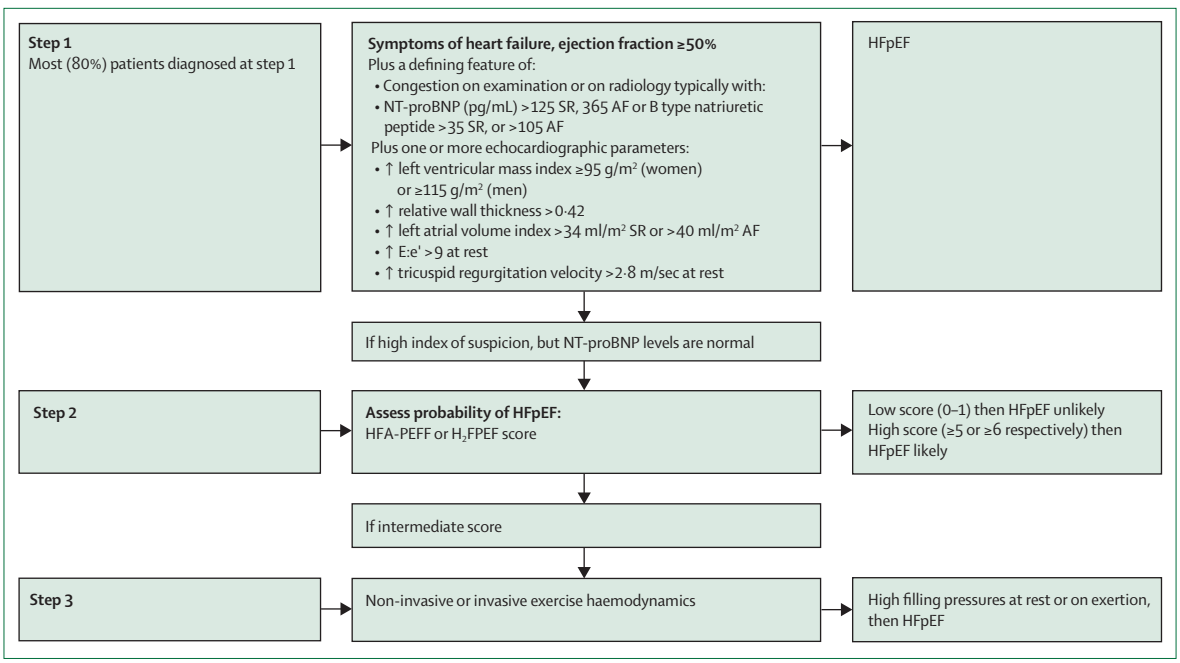
Step 1
Most (80%) patients diagnosed at step 1
Symptoms of heart failure, ejection fraction ≥50%
Plus a defining feature of:
• Congestion on examination or on radiology typically with:
• NT-proBNP (pg/mL) >125 SR, 365 AF or B type natriuretic peptide >35 SR, or >105 AF
Plus one or more echocardiographic parameters:
• ↑ left ventricular mass index ≥95 g/m² (women) or ≥115 g/m² (men)
• ↑ relative wall thickness >0·42
• ↑ left atrial volume index >34 ml/m² SR or >40 ml/m² AF
• ↑ E:e' >9 at rest
• ↑ tricuspid regurgitation velocity >2·8 m/sec at rest
HFpEF
If high index of suspicion, but NT-proBNP levels are normal
Step 2
Assess probability of HFpEF:
HFA-PEFF or H2FPEF score
Low score (0–1) then HFpEF unlikely
High score (≥5 or ≥6 respectively) then HFpEF likely
If intermediate score
Step 3
Non-invasive or invasive exercise haemodynamics
High filling pressures at rest or on exertion, then HFpEF

Figure 2: **HFpEF diagnostic algorithm**
AF=atrial fibrillation. E:e'=early diastolic mitral inflow velocity to early diastolic mitral annulus velocity. H_2FPEF=heart failure with preserved ejection fraction score. HFA-PEFF=Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology. HFpEF=heart failure with preserved ejection fraction. NT-proBNP=N-terminal pro-B type natriuretic peptide. SR=sinus rhythm.

The precise cutoffs for NT-proBNP and echocardiographic parameters are much debated. For example, recent publications have highlighted different cutoffs for NT-proBNP according to age and other factors.[47] Echocardiographic parameters and their cutoffs are often also confusing to generalists. Our recommendation is that patients with suspected heart failure are referred from primary care to secondary care via heart failure diagnostic pathways. These pathways allow referral to a process where heart failure diagnostic tests (NT-proBNP, electrocardiograms, and echocardiograms) are performed, and the results reviewed by a heart failure team. Clear feedback with respect to both heart failure diagnosis (HFpEF or HFrEF) and management plan can be provided to the primary care team.

Step 2: HFpEF risk scores

For approximately 20% of HFpEF cases where the NT-proBNP is normal but a high index of suspicion remains, HFpEF risk scores might be helpful. The two heart failure scores are the Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF) score (range 0–6),[48] and the heart failure with preserved ejection fraction (H_2FPEF) score (range 0–9).[49] Where the score is high (HFA-PEFF ≥5, H_2FPEF ≥6), then a diagnosis of HFpEF is likely, and when low (HFA-PEFF 0–1, H_2FPEF 0–1), HFpEF is unlikely.

Step 3: elevated filling pressure

In the event of intermediate probability (where HFA-PEFF score is 2–4 or H_2FPEF 2–5), step 3 is required to determine the presence of elevated filling pressures at rest or on exertion. The filling pressure can be established with non-invasive (with exercise stress echocardiography) or invasive haemodynamic exercise testing. In global clinical practice, the availability of both non-invasive and invasive haemodynamics is rare.

Mimics of HFpEF

The physician should, with clinical history and examination and investigation, rule out cardiac and non-cardiac mimickers of HFpEF. Cardiac mimickers are plentiful and include myocardial disease resulting in a thickened heart, including hypertrophic cardiomyopathy, infiltrative disorders (eg, amyloidosis, haemochromatosis, and sarcoidosis), and storage disorders (most notably Fabry disease); pericardial disease, such as constrictive pericarditis, primary valvular heart disease, pulmonary arterial hypertension (group 1 pulmonary hypertension) or lung disease-related pulmonary hypertension (group 3 pulmonary hypertension, which at first sight might be difficult to distinguish from pulmonary hypertension related to HFpEF); and high-output heart failure, and primary right ventricular failure (arrhythmogenic ventricular cardiomyopathy and right ventricular infarction). The echocardiogram should be examined for evidence of these cardiac mimickers, and this list should be systematically considered in every patient, but

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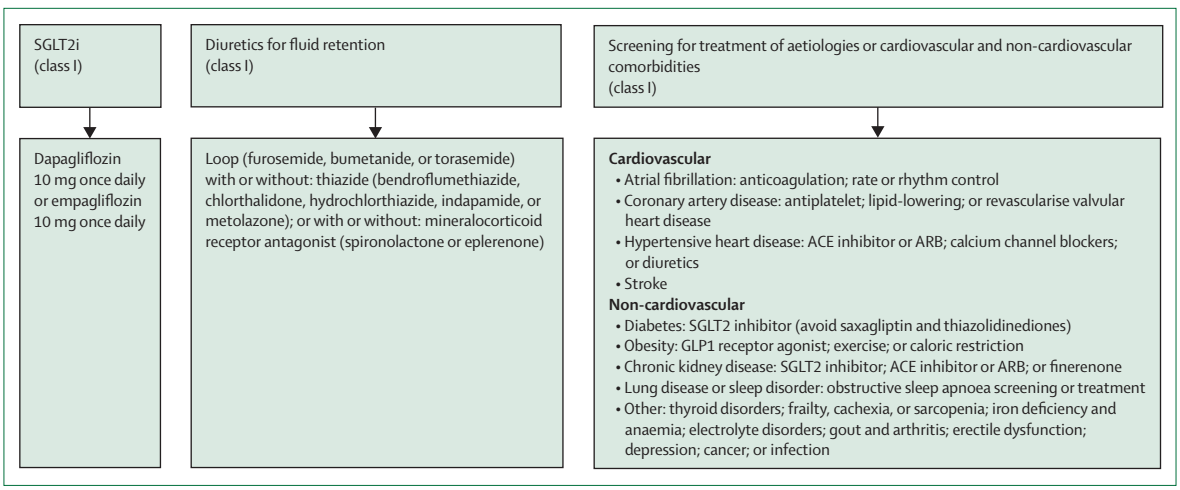
SGLT2i
(class I)
Diuretics for fluid retention
(class I)
Screening for treatment of aetiologies or cardiovascular and non-cardiovascular comorbidities
(class I)
Dapagliflozin
10 mg once daily
or empagliflozin
10 mg once daily
Loop (furosemide, bumetanide, or torasemide) with or without: thiazide (bendroflumethiazide, chlorthalidone, hydrochlorthiazide, indapamide, or metolazone); or with or without: mineralocorticoid receptor antagonist (spironolactone or eplerenone)
Cardiovascular
• Atrial fibrillation: anticoagulation; rate or rhythm control
• Coronary artery disease: antiplatelet; lipid-lowering; or revascularise valvular heart disease
• Hypertensive heart disease: ACE inhibitor or ARB; calcium channel blockers; or diuretics
• Stroke
Non-cardiovascular
• Diabetes: SGLT2 inhibitor (avoid saxagliptin and thiazolidinediones)
• Obesity: GLP1 receptor agonist; exercise; or caloric restriction
• Chronic kidney disease: SGLT2 inhibitor; ACE inhibitor or ARB; or finerenone
• Lung disease or sleep disorder: obstructive sleep apnoea screening or treatment
• Other: thyroid disorders; frailty, cachexia, or sarcopenia; iron deficiency and anaemia; electrolyte disorders; gout and arthritis; erectile dysfunction; depression; cancer; or infection

Figure 3: **The core strategies in HFpEF management**
ACEi=angiotensin-converting enzyme inhibitor. ARB=angiotensin-receptor blocker. HFpEF=heart failure with preserved ejection fraction. SGLT2i=SGLT2 inhibitor.

particularly among those with atypical features, such as younger age, relevant family history, or an absence of typical risk factors (eg, hypertension, diabetes, and obesity). Where doubt lies, additional imaging (eg, cardiac MRI or PET scanning) and laboratory work (eg, alpha-galactosidase for Fabry or iron studies for haemochromatosis) might be necessary.

HFpEF management

Non-pharmacological management

Figure 3 outlines the core strategies in HFpEF management. Management strategies for HFpEF include the identification and treatment of common comorbid conditions. This approach is often implemented in a hospital setting by a multidisciplinary team including nurses, medicine for the older physicians, pharmacists, and physiotherapists. Involvement of the general practitioner is important for ensuring seamless transition of care when the patient goes home, and for subsequent monitoring in an ambulatory clinic setting. Although clinical trials have shown the benefits of multidisciplinary care (especially by heart failure nurses)[50] in HFrEF, similar trials for HFpEF are yet to be completed. Notably, a trial that reported the benefits of cardiac rehabilitation in patients who were recently hospitalised with heart failure included about 50% of participants with HFpEF.[51]

Pharmacological management

A table of notable HFpEF drug trials is included in the appendix.

See Online for appendix

SGLT2 inhibitors

Recently (in 2021 and 2022), the first positive outcome trials in HFpEF were published. In the EMPEROR-Preserved[3] and DELIVER trials,[4] SGLT2 inhibitors reduced the composite of cardiovascular death and heart failure hospitalisations by 20% (hazard ratio [HR] 0·80; 95% CI 0·73–0·87; p<0·0001).[52] The ESC 2023 Heart Failure Guideline update has given SGLT2 inhibitor use for HFpEF a class 1a recommendation.[53]

Treatment of congestion

Relief from congestion with diuretics remains a cornerstone of HFpEF care for patients who are volume overloaded.[1] Therapy is initiated with loop diuretics with the type and dose depending on the severity of volume overload. For patients who do not show a sufficient diuresis with loop diuretics, either a thiazide or thiazide-like diuretic or mineralocorticoid receptor antagonists (MRAs) can be added, individually or in combination. The recommendation for MRAs (particularly spironolactone) comes from the signs of benefit from the TOPCAT trial.[54]

Treatment of cardiovascular and non-cardiovascular comorbidities

The core of therapeutic recommendations in HFpEF are focused on the treatment of underlying comorbidity and treating modifiable heart failure risk factors. Multiple cardiac and non-cardiac conditions, including hypertension, coronary artery disease, obesity, sleep apnoea, anaemia, diabetes, chronic kidney disease, atrial fibrillation, and chronotropic incompetence are all frequently associated with HFpEF, and might accelerate disease progression or contribute to functional intolerance. However, there is no evidence for HFpEF-specific management of these conditions. Pragmatic strategies for managing common comorbidities are addressed in the panel.

GLP-1 receptor agonists

The GLP-1 receptor agonist semaglutide was assessed for treatment of HFpEF in the STEP-HFpEF trial.[55] Semaglutide markedly improved health status and

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reduced weight. Reduction in NT-proBNP levels was approximately 15% greater with semaglutide than with placebo, suggesting a reduction in left ventricular filling pressures. Semaglutide reduced C-reactive protein. It will be important to see how these findings translate to hard endpoints in determining the role of GLP-1 agonism for HFpEF care.

Angiotensin receptor-neprilysin inhibitors and MRAs

Additional therapies might be considered for HFpEF, in keeping with the 2022 American College of Cardiology/American Heart Association (AHA) treatment guidelines,[56] although not included in the 2022 ESC Heart Failure Guideline update.[52] These agents include angiotensin-receptor blockers (ARBs), angiotensin receptor-neprilysin (ARN) inhibitors, and MRAs. Although none of these drugs reduced the primary outcomes in pivotal randomised controlled trials in HFpEF, subsequent analyses have suggested potential benefit in some patients with HFpEF. For example, a possible sign of reduction in heart failure hospitalisations was noted with the ARB candesartan in the CHARM-Preserved trial of patients with symptomatic heart failure and an ejection fraction greater than 40% (HR 0·84; 95% CI 0·70–1·00; p=0·047).[57]

In the PARAGON-HF trial, sacubitril with valsartan, when compared with valsartan, was associated with a modest (not statistically significant) reduction in the primary composite of total (first and recurrent) hospitalisations for heart failure and cardiovascular death (rate ratio 0·87; 95% CI 0·75–1·01; p=0·06).[54] Improvements in secondary endpoints including QoL, New York Heart Association functional class, and a composite of renal events among patients assigned to sacubitril with valsartan, was seen. Subgroup analyses suggested a greater benefit in women and in patients with an LVEF at or lower than the median value of 57%.[58] ARN inhibitors have been included in the 2022 AHA heart failure guidelines with a class 2b level of recommendation for the treatment of HFpEF.[55]

In the TOPCAT trial,[59] the MRA spironolactone, compared with placebo, did not reduce the primary outcome of time to cardiovascular death, aborted cardiac arrest, or heart failure hospitalisation in patients with heart failure and ejection fraction of 45% or more (HR 0·89; 95% CI: 0·77–1·04). Concerns were raised regarding patient selection and study conduct at some sites. A favourable treatment effect was seen in patients enrolled in the Americas, where recruitment criteria included elevated natriuretic peptide level (HR for primary composite: 0·82; 95% CI 0·69–0·98). This finding might be a better reflection of the effect of spironolactone in a true HFpEF population, with treatment benefits seemingly greatest in patients with an ejection fraction in the lower range.[60] MRAs have been included in the 2022 AHA Heart Failure guidelines with a class 2b level of recommendation for the treatment of HFpEF.[55]

***Panel*: Common concurrent conditions and the pragmatic therapeutic strategies**

- Hypertension: manage to guideline recommended targets, typically <130/80 mm Hg
- Coronary artery disease: antiplatelet therapy; intensify statin therapy if elevated LDL levels; and revascularisation for patients with angina or inducible ischaemia
- Obesity: glucagon-like peptide-1 receptor agonist semaglutide; aerobic exercise training and calorie restriction; obstructive sleep apnoea screening and treatment; consider bariatric surgery
- Diabetes: angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) for chronic kidney disease, or proteinuria; finerenone for proteinuria despite ACE inhibitor or ARB therapy
- Chronic kidney disease: ACE inhibitor or ARB for proteinuria; SGLT2 inhibitors; finerenone for diabetes and proteinuria despite ACE inhibitor or ARB therapy
- Atrial fibrillation: anticoagulated; consider rhythm control strategy initially if appropriate; aim for rate control to approximately 80–90 beats per min
- Chronotropic incompetence: avoid β-blockers unless there is a compelling indication

Serious adverse events relative to placebo in pivotal randomised control trials were uncommon. For example, in TOPCAT the incidence of hyperkalaemia was increased, but hypokalaemia decreased with no significant difference in serious adverse events overall. Drug discontinuation relative to placebo was equally uncommon. For example, in DELIVER, 5·8% of patients discontinued both dapagliflozin and placebo.[4] Both SGLT2 inhibtors and ARN inhibitors reduce adverse renal outcomes in patients with HFpEF.[51,61,62] Finally, there is synergism between these therapies. The principal side-effects of MRA are worsening renal function and hyperkalaemia, both of which are counteracted by SGLT2 inhibitors and ARN inhibitors.

Ongoing trials

The ongoing SPIRIT-HF (Spironolactone in the Treatment of Heart Failure; NCT04727073) and SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction; NCT02901184) trials will shed more light on the role of spironolactone in HFpEF. The non-steroidal MRA finerenone is being investigated in the ongoing FINEARTS-HF trial (NCT04435626). Similarly, the STEP-HFpEF DM (Semaglutide Treatment Effect in People with obesity and HFpEF and type 2 diabetes; NCT04916470) trial is ongoing.

The SUMMIT (a study of tirzepatide [LY3298176] in participants with heart failure with preserved ejection fraction and obesity; NCT04847557) trial is assessing the efficacy and safety of a dual glucose-dependent

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insulinotropic polypeptide and GLP-1 receptor agonists in patients with HFpEF and obesity. The HERMES trial (a research study to investigate how ziltivekimab works compared with placebo in people with heart failure and inflammation; NCT05636176) is assessing the effect of this novel therapeutic monoclonal antibody targeting the IL-6 ligand, in people living with HFpEF and who have concomitant inflammation.

In addition to pharmacological treatment, patients with HFpEF should be offered comprehensive guidance and support for implementing and maintaining lifestyle changes and self-care strategies. Programmes for managing chronic diseases and instruction in self-management might lower the probability of hospital admission for people with HFpEF.[1] Exercise training in patients with HFpEF improves outcomes, with benefits noted in exercise performance and QoL for patients living with HFpEF. These benefits are observed even in frail, older hospitalised patients with HFpEF.[63,64] Caloric restriction and exercise training had additive beneficial effects on exercise capacity and QoL in a randomised trial of 100 patients with obesity and HFpEF (SECRET trial).[65] The ongoing REHAB-HFpEF (physical rehabilitation for older patients with acute heart failure and preserved ejection fraction; NCT05525663) and REACH-HFpEF (a randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction) trials will examine the effect of lifestyle changes on HFpEF outcomes.

The management of HFpEF also requires careful consideration of which therapies should be avoided or withdrawn. Loop diuretic doses should be minimised once patients are euvolaemic and guideline directed medical therapy has been initiated (combinations of SGLT2 inhibitors, MRA, and ARN inhibitors). All these therapies have some diuretic effect. When low potassium is observed in HFpEF, the prescriber should (as a first step) consider starting or up titrating an MRA instead of prescribing potassium supplements if there is no contraindication to MRA (eg, estimated glomerular filtration rate <30 mL/min per 1·73m^2). Nitrates should be discontinued unless indicated for concurrent angina. In the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction) trial,[66] activity levels decreased progressively and significantly with increased doses of isosorbide mononitrate compared with placebo, and there was no benefit in terms of QoL or submaximal exercise capacity. There is no evidence for the efficacy of β-blockers in patients with HFpEF and LVEF over 50%. There does appear to be some benefit in patients with LVEF 41–49%.[67] β-blockers are used in HFpEF where there is a non-HFpEF indication, such as atrial fibrillation rate control, myocardial infarction, or angina. In one study, β-blocker withdrawal improved maximal functional capacity in patients with HFpEF and chronotropic incompetence.[68]

Conclusion

HFpEF represents at least 50% of all heart failure cases, and the poor QoL and high rates of hospitalisation and death represent a large unmet need. Due to an ageing population and increasing prevalence of comorbidities or disease drivers, such as obesity and diabetes, HFpEF prevalence is rising. The diagnosis of HFpEF can seem complex for the generalist, but by using natriuretic peptides and rest echocardiography (step 1 in our algorithm), a diagnosis can be made in most patients. Referral to heart failure specialists can be necessary for those where uncertainty persists. Current HFpEF management includes addressing comorbidities and consideration of pharmacological therapies, such as SGLT2 inhibitors.

Contributors

MCP conceptualised this seminar. All authors contributed to the design and content. PC, FHR, MMYL, and NMH wrote the paper and all authors helped with revisions. PC, FHR, MMYL, and NMH directly accessed and verified the underlying data. All authors had full access to the data in the study and accept responsibility to submit for publication.

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